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ORIGINAL PAPER

The impact of intravenous immunoglobulin on kidney functions and thromboembolic events in dermatology patients

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Abstract

Although intravenous immunoglobulin (IVIG) treatment is generally well tolerated, some adverse effects, ranging from mild to severe, can occur. Nephrotoxicity and thromboembolism are the significant adverse effects of IVIG. However, data on the frequency of thromboembolism and the impact of continuous treatment on renal functions in dermatology patients is limited. This retrospective study was conducted in a cohort of patients who received at least one high-dose (2 g/kg) IVIG cycle due to different dermatological indications, including pemphigus vulgaris, bullous pemphigoid, Stevens-Johnson syndrome, pyoderma gangrenosum, hidradenitis suppurativa and toxic epidermal necrolysis at a university hospital. Demographic and clinical information, thromboembolic events, and kidney function tests were systematically extracted from patient records. The study included 48 patients who received a total of 196 IVIG cycles with a mean dose of two cycles (range 1–41). A significant difference in renal function was observed between baseline and post-treatment in patients who received three or more IVIG cycles. In comparison, no significant difference was found in those receiving one or two IVIG cycles. Five patients (10.4%) experienced a decline of ≥ 20% in the estimated glomerular filtration rate (eGFR). In multivariate analysis, cumulative IVIG dose emerged as the sole independent predictor for a ≥ 20% decline in eGFR (OR 1.61, 95% CI 1.05–2.46, p = 0.02). Thromboembolism occurred in five patients (10.4%), with three cases arising during the first cycle. Thromboembolism, especially during the initial IVIG cycles, and decline in kidney functions related to cumulative IVIG dose were the common and significant side effects in this cohort of dermatology patients.

Keywords Intravenous immunoglobulin · Dermatology patients · Side effects · Thromboembolism · Kidney function

Introduction

Intravenous immunoglobulin (IVIG) is a sterile, highly purified immunoglobulin G (IgG) derived from the pooled plasma of thousands of screened individual donors. In dermatology, IVIG is mainly used in toxic epidermal necrolysis, scleromyxedema, and autoimmune disorders, including autoimmune blistering diseases, dermatomyositis, systemic vasculitis, and systemic lupus erythematosus [1]. IVIG has also been demonstrated to be an effective treatment for a few cases of refractory pyoderma gangrenosum, atopic dermatitis, autoimmune urticaria, and livedoid vasculopathy [1, 2]. Only one cycle of IVIG treatment is used in toxic epidermal necrolysis, while long-term therapy may be required for other dermatological conditions [1].

Intravenous immunoglobulin (IVIG) treatment is generally well tolerated, but some adverse effects, ranging from mild to severe, can occur. Rare but serious side effects, such as thromboembolic events and nephrotoxicity, require

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careful monitoring and management; otherwise, they could lead to fatal outcomes [3, 4]. Previous studies have suggested that the incidence of thromboembolism associated with IVIG may be as high as 16.9% in non-dermatological patients [5]. Studies have rarely described thromboembolic events in patients with autoimmune bullous disease [6, 7]. These patients may be at increased risk due to factors such as systemic inflammation, advanced age, comorbid conditions, and the use of systemic steroids. Therefore, more research is needed in this area.

Typical nephrotoxicity of IVIG is acute kidney injury, especially that occurs due to IVIG formulas that contain sucrose [8]. Some studies proposed that the nephrotoxicity of IVIG may extend behind the expected duration. Continuous intravenous immunoglobulin treatment has been shown to induce tubular macrovacuoles associated with lower creatinine clearance in kidney transplant patients [9]. In a retrospective analysis of 166 patients who received IVIG treatment for neurological indications, a ≥ 20% decline in glomerular filtration rate was found in 10% of the patients at the end of 12 months of treatment duration [10]. However, the long-term effects of IVIG treatment on kidney functions in dermatology patients with multiple comorbidities and polypharmacy have not been well documented. Our study aimed to address the impact of intravenous immunoglobulin on kidney functions and thromboembolic events in dermatology patients.

Material and methods

Patients

The study included 48 patients who received at least one cycle of IVIG treatment at a dose of 2 g per kg body weight for dermatological indications between January 2017 and August 2024 at the Dermatology Department of our university hospital. Patients without baseline laboratory tests and those treated with IVIG lower doses than 2 g/kg body weight were excluded from the study.

Laboratory evaluations

All patients were evaluated for serum IgA levels, baseline kidney functions, urinalysis, and hepatitis serology tests before initiating IVIG treatment.

Infusion protocol

Since IVIG products are costly and not always available, they were obtained from different manufacturers instead of a single one. The same brand was used for each patient unless there were any side effects. Thirteen patients were required to switch from an IVIG product to a different one. Among the IVIG prescriptions, 47.4% were Flebogamma (sorbitol-stabilized), 25% were Octagam (maltose-stabilized), and 18.8% were Nanogam (glucose-stabilized). The remaining brands were Immutect (glycine-stabilized), Ig Vena (maltose-stabilized), Genivig (maltose-stabilized) and Privigen (L-proline-stabilized). Sucrose-containing IVIG preparations were not used. Intravenous immunoglobulin was administered over five days in all patients. On the first day of treatment, 40 mg methylprednisolone, 1000 mg acetaminophen, and 45.5 mg phenyramine hydrogen maleate were administered intravenously to patients as premedication. During the infusion period, 1000 cc saline intravenous infusion and subcutaneous enoxaparin sodium 40 mg were given once daily. The initial interval of the treatment cycles was four weeks for the continuous treatment. The intervals were extended to 6–8 weeks before discontinuing.

Outcomes

Control kidney function tests were requested within the first 5 days after the last treatment. Demographic and clinical information, kidney function tests, including estimated glomerular filtration rate (eGFR) and creatinine before and after treatment, were retrospectively recorded from the patient files. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [11].

Patients were divided into two subgroups according to the total number of IVIG cycles received: one or two cycles (n:26) and greater than or equal to three (≥ 3, n:22).

According to the study by Levine et al., we used a cut-off value of ≥ 20% decline in eGFR from baseline to determine the significant change after IVIG treatment [10]. The patients who experienced a significant decrease in eGFR were followed up three months after the last IVIG cycle.

In addition, thromboembolic events occurring during and after IVIG treatment were recorded.

This study was approved by the Dokuz Eylül University Noninvasive Clinical Studies Ethics Committee (Date: 07.02.2024, Decision No: 2024/05–22).

Statistical analyses

Descriptive statistics for the data included mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The distribution of variables was measured by Kolmogorov–Smirnov and Shapiro–Wilk tests. An independent sample t-test was used to analyze quantitative independent data with normal distribution. The Mann–Whitney U test was used to analyse quantitative independent data with non-normal distribution. The chi-square test was used to analyse qualitative independent data, and the Fischer's

exact test was used when chi-square test conditions were not met. Spearman correlation analysis was used in correlation analysis. Predictors of the decline in eGFR were evaluated using the logistic regression analysis. Variables that were thought to be effective on renal function were included in the multivariate regression model. Results are provided as odds ratios with 95% confidence intervals. The IBM SPSS Statistics 28.0.0 program was used in the study. All tests were two-tailed, and p-values less than 0.05 were considered statistically significant.

Results

Patient characteristics

The study cohort of 48 patients included 26 (54.2%) females and 22 (45.8%) males. The mean age of the patients was 56.8 ± 17 years. The majority of the patients (64.6%) were diagnosed with pemphigus vulgaris, followed by bullous pemphigoid (12.5%), Stevens-Johnson syndrome (8.3%), pyoderma gangrenosum (6.3%), hidradenitis suppurativa (6.3%) and toxic epidermal necrolysis (2.1%). The detailed patient characteristics are given in Table 1.

The mean serum IgA level of the patients was 298.9 ± 214.3 mg/dl, ranging between 104 and 1055 mg/dl. The mean eGFR of patients was 100.6 ± 23.3 ml/min (range 35.0–153.0), and the mean creatinine level was 0.71 ± 0.23 mg/dl (range 0.22–1.41) before IVIG treatment. The baseline eGFR levels were lower than 60 ml/min in four patients. According to hospital records, estimated glomerular filtration rates were less than 60 ml/min for at least three months in two patients, while the other patients' data were unknown.

The patients received a total of 196 IVIG cycles with a mean dose of two cycles (range 1–41). The age and gender distribution of the patients did not differ significantly between the groups receiving one or two cycles and ≥ 3 cycles of IVIG. The comparison of the patient characteristics between the treatment groups is given in Table 1.

Table 1 Patient characteristics

	All patients (n:48), n (%)		1–2 cycles of IVIG (n:26), n (%)		≥ 3 cycles IVIG (n:22) n (%)		p
Age (years) Mean ± SD	54.8 ± 17.1		58.7 ± 16.9		50.3 ± 16.9		0.09
Gender							
Female	26	(54.2)	13	(50.0)	13	(59.1)	0.52
Male	22	(45.8)	13	(50.0)	9	(40.9)	
Dermatologic disease							
Pemphigus vulgaris	31	(64.6)	12	(46.1)	19	(86.3)	0.004
Bullous pemphigoid	6	(12.5)	6	(23.0)	0	(0)	0.025
Stevens-Johnson syndrome	4	(8.3)	4	(15.4)	0	(0)	0.11
Toxic epidermal necrolysis	1	(2.1)	1	(3.8)	0	(0)	1.0
Pyoderma Gangrenosum	3	(6.3)	2	(7.7)	1	(4.5)	1.0
Hidradenitis Suppurativa	3	(6.3)	1	(3.8)	2	(9.0)	0.58
Comorbidities							
Diabetes	16	(33.3)	11	(42.3)	5	(22.7)	0.15
Hypertension	17	(35.4)	13	(50.0)	4	(18.2)	***0.02***
Coronary heart disease	5	(10.4)	4	(15.4)	1	(4.5)	0.22
Chronic renal failure	4	(8.3)	4	(15.4)	0	(0.0)	0.07
Dyslipidemia	13	(27.1)	8	(61.5)	5	(38.5)	0.42
Smoking							
(–)	30	(62.5)	18	(69.2)	12	(54.5)	0.29
(+)	18	(37.5)	8	(30.8)	10	(45.5)	
Concomitant systemic therapy							
Systemic steroid	40	(83.3)	19	(73.1)	21	(95.5)	***0.03***
Rituximab	12	(25.0)	5	(19.2)	7	(31.8)	0.31
Azathioprine	12	(25.0)	3	(11.5)	9	(40.9)	***0.01***
Nephrotoxic drugs	20	(41.7)	13	(65.0)	7	(35.0)	***0.20***

Renal effects

No patient developed acute renal failure after IVIG infusion. In the group receiving one or two cycles of IVIG, the creatinine value after the last treatment did not change significantly compared to the baseline [0.77 mg/dl (range 0.37–1.41) vs 0.66 mg/dl (range 0.47–1.25), p 0.122]. In the group receiving ≥ 3 cycles of IVIG, the creatinine value after the last treatment increased significantly compared to the baseline level [0.61 mg/dl (range 0.22–0.95) vs 0.70 mg/dl (range 0.31–1.10), p:0.002]. In the group receiving one or two cycles of IVIG, the eGFR value did not change significantly [105 ml/min (range 35–125) vs 105 ml/min (range 40–120) p > 0.091] after the last treatment compared to before treatment. In the group receiving ≥ 3 cycles of IVIG, the eGFR value showed a significant decrease after the last treatment compared to before [107 ml/min (range 80–153) vs 100 ml/min (range 56–120), p: 0.001].

When we evaluated the correlation between the creatinine value changes and the total number of IVIG cycles, there was a statistically significant positive correlation (r: 0.537, p < 0.001) (Fig. 1). In addition, there was a negative correlation between the eGFR level changes and the total number of IVIG cycles (r: − 0.540, p: < 0.001) (Fig. 2).

In five (22.7%) of 22 patients who received ≥ 3 cycles of IVIG treatment, at least a 20% drop in eGFR was observed. No statistically significant difference was determined between the examinations of these patients at 3-month intervals after the end of treatment (76 ml/min (range 56–120) versus 85 ml/min (range 69–87), p: 0.46, respectively). The comparison of the patient characteristics between the patients with ≥ 20% decline in eGFR and those without is presented in Table 2.

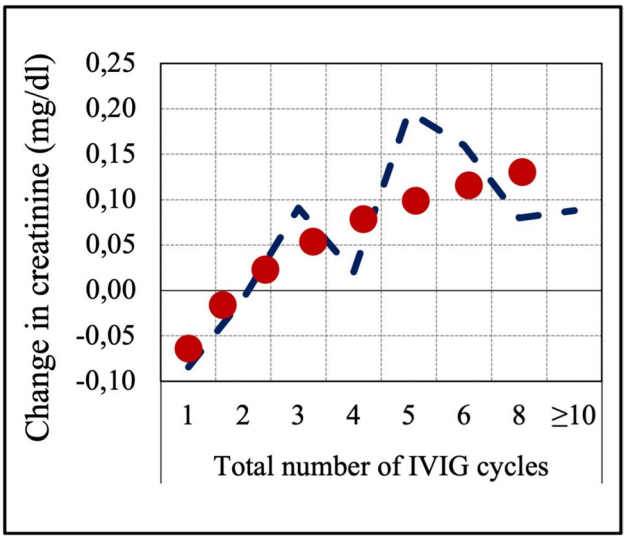


Fig. 1 Correlation between the change in creatinine and the total number of IVIG cycles

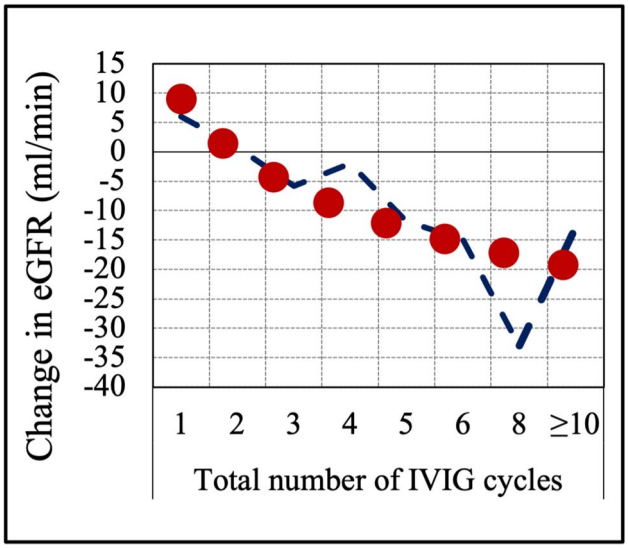


Fig. 2 Correlation between the change in eGFR and the total number of IVIG cycles

In univariate analysis, cumulative IVIG dose was associated with a ≥ 20% decline in eGFR. In the multivariate analysis of gender, age, diabetes mellitus, hypertension, steroid and nephrotoxic drug usage, and total number of IVIG cycles, cumulative IVIG dose was the sole independent predictor for a ≥ 20% decline in eGFR. The logistic regression analysis of the factors affecting the decline in eGFR is given in Table 3.

Thromboembolic events

Thromboembolism related to IVIG treatment was observed in five (10.4%) patients. Three patients (6.25%) developed deep vein thrombosis (one with thrombophlebitis), and one (2.1%) experienced only thrombophlebitis. A pulmonary embolism was seen in one patient (2.1%). Four of the five thromboembolic events occurred in the initial (first or second) cycles. The details of patients who experienced thromboembolic events and imaging findings are given in Table 4. There was no statistically significant difference in the mean age between patients who developed IVIG-related thromboembolism and those who did not, with ages of 57 years and 56.8 years, respectively (p = 0.98). Additionally, when we examined the gender distribution and the frequency of comorbidities, we found no statistically significant differences between the groups with and without thromboembolism. The outcome of the thromboembolic events was favorable in all patients after discontinuing IVIG infusion and appropriate treatment.

Table 2 The comparison of the patient characteristics between the patients with ≥ 20% decline in eGFR and those without

	Patients with ≥ 20% decline in eGFR (n:5)		Patients without ≥ 20% decline in eGFR (n:43)		p
Age (years) Median(range)	62 (19–75)		54 (10–86)		0.48[t]
Gender n, %					
Female	4	80%	22	51.2%	0.3[X2]
Male	1	20%	21	48.8%	
Total number of IVIG cycles	8 (3–41)		2 (1–18)		**0.007**[t]
Comorbidities (n, %)					
Diabetes	2	40%	14	32.6%	1.0[X2]
Hypertension	2	40%	15	34.9%	1.0[X2]
Coronary heart disease	1	20%	4	9.3%	0.4[X2]
Chronic renal failure	0	0%	4	9.3%	1.0[X2]
Dyslipidemia	0	0%	13	33.3%	0.3[X2]
Smoking					
(–)	2	40%	28	65.1%	0.3[X2]
(+)	3	60%	15	34.9%	
Concomitant systemic therapy					
Systemic steroid	4	80%	36	83.7%	1.0[X2]
Rituximab	1	20%	11	25.6%	1.0[X2]
Azathioprine	2	40%	10	23.3%	0.5[X2]
Nephrotoxic drugs	3	60%	17	39.5%	0.6[X2]

[t]Independent sample t test

[X2]Chi-square test (Fischer's test)

Table 3 The logistic regression analysis of the factors affecting the decline in eGFR

	Univariate analysis			Multivariate analysis		
	OR	%95 CI	p	OR	%95 CI	p
Gender (Ref:M)	0.26	0.02–2.53	*0.24*	0.44	0.01–13.18	*0.64*
Age	1.004	0.95–1.06	*0.87*	1.19	0.99–1.44	0.055
Diabetes mellitus	1.38	0.20–9.22	*0.73*	0.39	0.00–150.74	0.75
Hypertension	1.24	0.18–8.28	*0.82*	0.37	0.00–246.37	0.76
Steroid usage	0.77	0.078.04	*0.83*	0.01	0.00–1.42	0.07
Nephrotoxic drug usage	2.29	0.34–15.19	*0.38*	0.40	0.01–12.49	0.60
Total number of IVIG cycles	1.22	1.008–1.48	***0.04***	1.61	1.05–2.46	**0.02**
Baseline eGFR	1.02	0.97–1.07	*0.38*	1.06	0.98–1.15	0.10

Logistic regression analysis (Backward LR)

CI confidence interval, *eGFR* estimated glomerular filtration, *M* male, *OR* Odds ratio

Discussion

Our study highlights two significant side effects of IVIG treatment in dermatology patients. The first is thromboembolism, which mostly occurs during the initial cycles of the treatment. The second is the cumulative impact of IVIG treatment on kidney functions, which is a previously unrecognized side effect in these patients.

In our dermatology cohort, no patient experienced acute renal failure, the most typical nephrotoxicity related to IVIG treatment. Gürcan et al. reported acute renal failure after IVIG infusion in one of 174 patients diagnosed with pemphigus or pemphigoid. The patient received a sucrose-containing IVIG product as a stabiliser and recovered after hemodialysis [12]. Most of the reported renal toxicity events have been associated with sucrose-containing IVIG preparations,

Table 4 Patients experienced a thromboembolic event after IVIG treatment

Age(years), gender	Indication of IVIG therapy	Risk factors	IVIG cycle of side effect	Day of side effect	Imaging findings (doppler ultrasound/ computer tomography)
56, M	Pemphigus vulgaris	Smoking	4	4th day	Deep vein thrombosis of the left upper extremity and superficial thrombophlebitis in the left basilic vein
19, F	Pemphigus vulgaris	–	2	1st day	Deep vein thrombosis of the superficial femoral vein and the popliteal vein of the left lower extremity
51, F	Pyoderma gangrenosum	DM, HL, CAD, asthma, smoking, immobility	1	3rd day	Deep vein thrombosis of the superficial femoral vein in the right lower extremity
78;F	Pemphigus vulgaris	DM, HT, CKD, immobility	1	–	Left pleural effusion, pulmonary atelectasis in the left upper lobe (inferior lingular segment) and left lower lobe (basal segment), compatible with pulmonary embolism
81;F	Stevens- Johnson syndrome	DM, HT, immobilitiy	1	4th day	Superficial thrombophlebitis of the left cephalic vein

DM Diabetes mellitus, *HT* Hypertensions, *CKD* chronic cardiac disease, *F* Female, *M* Male

which damage the kidney by osmotic nephrosis [8, 13, 14]. Baseline renal insufficiency, older age, hypertension, diabetes mellitus, and hypovolemia are the reported risk factors for severe nephrotoxicity requiring hemodialysis [8]. Rarely a few acute renal failure events related to products containing glycine, maltose and glucose have been reported in the literature [13, 15]. Since we did not utilize sucrose-containing preparations, no acute renal failure occurred in any of our patients.

The long-term effect of IVIG treatment on kidney functions has not been previously documented in dermatology patients. Our results showed that multiple cycles (three or more) of IVIG treatment affected kidney functions, while one or two cycles of IVIG treatment did not. Kidney function change correlated with the total number of IVIG cycles. However, only five (22%) of the patients who received ≥ 3 cycles of IVIG treatment developed a significant drop in eGFR. The multivariate analysis determined that the total number of IVIG doses was the sole predictive factor for at least a 20% decline in eGFR. In these five patients, no statistically significant difference was determined between the examinations at 3-month intervals after and the end of treatment. Levine et al. demonstrated a greater than 20% decrease in glomerular filtration rate in 10% of 166 patients who underwent IVIG treatment for neurological indications over 12 months. Four brands of IVIG products, one of which contained sucrose, were included in their study. The decrease in GFR was not related to the IVIG brand used [10]. The lower rate in their study than our results may be due to the exclusion of the patients using systemic steroids and those with a prior history of renal failure. A previous study documented the presence of tubular macrovacuoles linked to chronic tubulointerstitial damage in patients who received four cycles of IVIG treatment following renal transplantation [9]. Similarly, another study evaluated the clinical and histological safety of the non-sucrose-based IVIG preparations in kidney transplant patients (n:75) compared with the control group who did not receive IVIG treatment (n:75). At three months of post-transplantation, a higher rate of tubular vacuolisation was observed in the non-sucrose based IVIG treated group. Compared to amino-acid-stabilized formulations, carbohydrate-stabilized IVIG products were independently associated with tubular macrovacuoles. They concluded that sucrose-free IVIG treatment was not associated with acute renal failure but with an increased frequency of tubular macrovacuoles [16]. The negative cumulative effect of the non-sucrose-based IVIG preparations in the kidney functions in our study may be explained by the same mechanism leading to alterations of proximal tubular functions. Further studies are needed to confirm the renal effects of long-term use of sucrose-free IVIG preparations and whether these effects are reversible.

Thromboembolic events following IVIG therapy occurred in 10.4% of our patient cohort. This rate is quite high considering that no thromboembolism was reported in previous studies consisting of patients with dermatologic indications [6, 12, 17]. Mignogna et al. did not observe any thromboembolic complications in 10 patients, seven of whom had predisposing factors, during the administration of 133 IVIG cycles for autoimmune bullous diseases. They suggested their protocol, including hydration of patients before and after infusions and the use of aspirin and subcutaneous calcium heparin, can reduce the risk of such life-threatening complications [17]. Similarly, in the

study of 174 patients with pemphigus or pemphigoid under IVIG therapy no patient developed thromboembolism [12]. In the retrospective analysis of 123 pemphigus patients treated with a combination of IVIG, a cytotoxic drug and mitochondrion-protecting drug, three patients developed thromboembolic events, including deep venous thrombosis, stroke, and pulmonary embolism [4]. The high rate of thromboembolic complications in our patients may be due to their higher mean age than those reported (56 years vs. 52/55/50 years, respectively) and the included patients diagnosed with Stevens-Johnson syndrome and pyoderma gangrenosum, which could lead to immobilization due to excessive pain. In studies evaluating various patient groups, the findings regarding the thrombosis risk associated with IVIG treatments appear contradictory. A systematic review and meta-analysis encompassing 31 randomized controlled trials found no risk of thromboembolism in patients receiving IVIG treatment compared to control patients. However, the trials mainly included middle-aged or younger participants. Therefore, the authors cautioned against generalizing the results to older or higher-risk patients [18]. Similarly, Rotrosen et al. did not find any significant difference in the incidence of dermatomyositis-associated venous thromboembolism between patients receiving and not receiving IVIG [19]. On the other hand, a recent systematic review evaluating the adverse reactions of IVIg therapy in patients with neurological disease reported an odds ratio of 3.33 (1.34–8.30, $p=0.0097$) for venous thromboembolism within 30 days after exposure to IVIG. The thromboembolic risk was found to be higher [OR: 10.5 (95% CI 1.91–57.58)] in patients with ≥ 4 cardiovascular risk factors [20]. Like our results, IVIG-related thrombotic complications, including deep venous thrombosis, pulmonary embolism, myocardial infarction, and stroke, occurred in 13% of the patients with autoimmune disorders followed up in a department of internal medicine [21]. Older age, hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, and thrombophilia were identified as predisposing factors for IVIG-associated thromboembolic events [20, 21]. In addition, patients with autoimmune bullous diseases are at an increased risk of thromboembolism due to factors such as hospitalisation, higher rates of systemic infections, corticosteroid therapy, and systemic inflammation [22, 23]. The use of intravenous immunoglobulin (IVIG) treatment may further elevate the risk of thromboembolism, particularly during the initial cycles of treatment, as in our patients, when inflammation is most active.

The limitations of our study include a small patient sample size, an uncontrolled retrospective design, and the heterogeneous diagnosis among patients. The high cost of IVIG treatment and its off-label approvals in various indications contributed to the limited number of patients. Furthermore, due to the retrospective nature of the study, we were unable to assess the underlying thromboembolic risk factors within the patient population. Despite these limitations, our findings are valuable in increasing awareness of thromboembolism and decline in eGFR related to IVIG treatment in dermatology patients, most of whom are elderly and have multiple comorbidities.

In conclusion, our dermatology cohort demonstrated a notable decline in eGFR and an increased incidence of thromboembolism associated with IVIG treatment. We suggest that patients should be closely monitored during IVIG infusion, especially during the initial cycles, regarding the signs of thromboembolic events. Furthermore, those undergoing long-term IVIG therapy should be closely observed for cumulative impacts on renal function.

Author contributions Ceylan Avcı and Aygün Talibova extracted the data from patient files. Ceylan Avcı wrote the first draft of the manuscript. Cihan Heybeli evaluated the significance of the change in renal functions related to IVIG treatment. All authors added critical intellectual content and read and approved the final version of the manuscript.

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Data availability The data analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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